

EXHIBIT G



Sullivan
9-24-86

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Cliff
In re application of: Bonnie Davis

Serial No.: 819,141

Group No.: 125

Filed: January 15, 1986

Examiner: Friedman

Sullivan
9-25-86
FOR METHOD OF TREATING ALZHEIMER'S DISEASE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

RECEIVED

SEP 17 1986

SIR:

AMENDMENT RESPONSIVE TO OFFICE ACTION
OF APRIL 10, 1986

GROUP 120

Please amend the application as follows:

IN THE SPECIFICATION

At page 1, line 12, change "anesth. scand." to read --
Anesth. Scand.--.

Page 2, line 29, change "from" to read --form--.

Page 2, line 33, correct spelling of --aids--.

IN THE CLAIMS

Claim 1, line 1, delete "and diagnosing".

R E M A R K S

The application is amended to meet the Examiner's rejection under 35 USC 112 by deletion of reference to diagnosis. This amendment is made without prejudice to the possibility of filing a divisional or continuation-in-part application directed to

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

JOSEPH H. HANDELMAN

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Date: SEPTEMBER 9, 1986

Joseph H. Handel
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diagnosis in due course.

The amendments to the specification correct obvious typographical errors.

Alzheimer's disease is a major and growing problem in our society (see the paper by Hershenson & Moos in July 1986 Journal of Medical Chemistry submitted herewith). It is estimated that there are over 1,000,000 sufferers of this disease in the United States alone. Symptoms include depression, intellectual decline, memory loss, speech difficulties and muscular spasms. Little is known about the root cause of the condition and although useful results have been reported in some cases by treatment with physostigmine, its poor therapeutic index is likely to preclude its widespread use and there is no generally effective treatment available. As noted in an article by Kendall et al, submitted herewith, (J Clin Hos Pharmac (1985) 10 327-336), "The theoretical possibility of developing a long acting preparation of an agent with good brain penetration and possibly some selectivity of action towards the relevant cortical cholinergic system, must be seen as a major challenge for researchers working on Alzheimer's disease". Applicant currently has experiments underway using animal models which are expected to show that treatment with galanthamine does result in an improvement in the condition of those suffering from Alzheimer's disease. It is expected that data from this experimental work will be available in two to three months and will be submitted to the Examiner promptly thereafter. Furthermore, galanthamine is currently being used in Europe to assist in post-operative recovery from anaesthesia and so is unlikely to suffer the problems of possible toxicity encountered with physostigmine (Acta Anesth Scand (1980) 21:166).

The rejections under 35 USC 103 are respectfully

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traversed. The rejection is based on two Chemical Abstract references noted in the specification. The first, by Kraus, is an abstract of a paper published in the Journal of Highest Nervous Activity Volume 24 (1974). The second is an article by Chaplygina and Ilyuchenok. Applicant has had translations of each of the original papers prepared and these are submitted herewith.

The Kraus article related to an investigation of the effects of various chemicals on short-term memory and the activity of the hippocampus in normal dogs. It concluded that the effect of galanthamine was about the same as that of strychnine and lower than that of phenamine and ethimizol.

The Chaplygina article describes work done on restoration of conditioned reflexes after memory in mice had been destroyed, for example, by electro-shock.

The Examiner's comment on this art, namely that it "teaches activities for the instant agent that would have value in treating the effects of Alzheimer's disease" is not entirely clear. However, apparently what the Examiner means is that since these articles indicate that galanthamine has an effect on improving short-term memory and on restoring memory after it has been destroyed, it would be useful in treating Alzheimer's disease. This is a non sequitur.

The mechanism of memory and indeed many brain functions are still only hazily understood at best. One cannot predict with any degree of confidence what the effect of any given chemical on a particular brain function or brain condition may be. While it is true that studies have shown that impairment of memory may result from certain specific factors varying from brain damage, though diminution of blood flow as a result of arteriosclerosis in brain arteries to chemical effects such as

thiamine deficiency in causing Wernicke-Korsakoff syndrome, the cause of "normal" establishment of memory and forgetfulness is still not understood. It is true that in Alzheimer's disease, there is memory loss. However, this is apparently associated with physiological changes in the brain including degeneration of nerve cells in the frontal and temporal lobes, damage in the neural pathways to the hippocampus and the creation of neurofibrillary tangles in nerve cells. There is no way of predicting that because a chemical may have an effect on memory in a normal brain (which is what is indicated in the cited references) it would have any effect on a brain that has suffered such physiological changes. To say that simply because a particular drug has some effect on a symptom caused by one underlying condition, it will have a useful effect on another underlying condition is clearly wrong. To predict that galanthamine would be useful in treating Alzheimer's disease just because it has been reported to have an effect on memory in circumstances having no relevance to Alzheimer's disease would be as baseless as predicting that one should treat impaired eyesight due to diabetes with drugs effective in ameliorating impaired vision due to other causes such as glaucoma. In fact, since the animals used in the studies of Kraus and Chaplygina were normal, an even more pertinent analogy can be made. The prediction that galanthamine would be useful to treat Alzheimer's disease because it is known to have an effect on memory in normal animals is as baseless as a prediction that impaired eyesight due to diabetes would respond to devices (eyeglasses) or treatments (eye exercises) known to improve the vision of normal persons. In diabetes, impaired eyesight is most often the result of bleeding from the retina and would not be improved by eyeglasses or such treatments.

In fact, the art cited in the present case does not even provide the basis for speculation at this level. Turning first to the Kraus article, the learning task utilized in this study is poorly described, but seems to be the effect of a delay between the presentation of a stimulus and the time in which a nondiseased dog is allowed to make its conditioned response. The Alzheimer's patient suffers from problems in language, praxis, naming, and the ability to learn new information. It is the constellation of these abnormalities that gives the Alzheimer's patient a pattern of dementia that is being regarded as relatively diagnostic. Thus, improving a small aspect of memory function in a nondiseased dog whose brain has neither the anatomical nor biochemical lesions of Alzheimer's disease is far from a valid test of a medication for Alzheimer's disease. It is not surprising that positive results from the experiments performed by Kraus are found for a class of compounds (amphetamine like) that are ineffective in Alzheimer's disease. Recently models have been established with animals with selective neurotransmitter and anatomic deficits that mimic Alzheimer's disease, that have some validity, and could be anticipated to have predictive ability. Such is not the case for this conditioned learning paradigm applied to intact animals.

Apart from galanthamine, three drugs (ethimazol, phenamine and strychnine) are referred to by Kraus as being useful in their effects on short-term memory. Ethimazol acts by increasing cAMP, a major effect of methamphetamine as well (Biull Exp Biol Med (1977) 83:185). Phenamine is methamphetamine. Methamphetamine has been directly tested in patients with Alzheimer's dementia; it has absolutely no effect (Psychopharmacology (1977) 52:251, J Am Geriat Soc 1977 25:1). Strychnine is a convulsant which stimulates brain non-

specifically (Gilman AG, Goodman LS, Rall TW, Murad F, eds., The Pharmacological Basis of Therapeutics, Macmillan Publ. Co., New York, 1985, p. 582). Pentylenetetrazol (Metrazol), a compound with convulsant and stimulant properties analogous to those of strychnine, does not improve cognitive function in Alzheimer's patients (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177). Thus, the ability of a drug to enhance memory in the experiments performed by Kraus does not indicate that the drug will be of use in Alzheimer's disease.

The teaching of the Chaplygina article does not take matters any further forward. It teaches that galanthamine reverses the amnesia-producing effects of scopolamine. However, this would be expected of an anticholinesterase. Nothing in this teaching leads to an expectation of utility against Alzheimer's disease. There are many anticholinesterase drugs available but Alzheimer's disease is still regarded as being effectively untreatable.

Applicant carried out a survey of drugs which were reported in the literature to have been useful in enhancing short-term memory over the period 1973-1976 and followed this up with a survey of whether any of them has subsequently been reported as having been tried in connection with Alzheimer's disease. The results are as follows:

39 compounds were reported to facilitate memory in various studies of animals and humans without brain lesions: adrenocorticotrophic hormone (Behav Biol (1976) 16:387, J Pharm Pharmac (1977) 29:110), ACTH 4-10 (J Pharm Pharmac (1977) 29:110, Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41, Physiol Behav (1975) 14:563, Pharmacol Biochem Behav (1974) 2:663, Physiol

Behav (1974) 13:381, Sachar EJ, ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), adenosine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), amphetamine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory MIT Press, Cambridge, Mass., 1976, p.483 Pharmacol Biochem Behav (1976) 4:703, Pharmacol Biochem Behav (1974) 2:557, Behav Biol (1977) 20:168), apovincamate (Arzneim-Forsch (1976) 26:1947), caffeine (Acta Physiol Pharmacol Bulg (1976)2:66), desglycine lysine vasopressin (Sachar EJ, ed, Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), echinopsin (Acta Physiol Pharmacol Bulg (1976) 2:66), fluorothyl (Physiol Behav (1975) 14:151), glutamate (Brain Res (1974) 81:455), heavy water (Naturwissenschaften (1974) 61:399), histamine (Acta Physiol Pharmacol Bulg (1976) 2:49), imidazole (Acta Physiol Pharmacol Bulg (1976) 2:49), imipramine (Pharmacol Biochem Behav (1974) 2:663), isoprenaline (Pharmacol Biochem Behav (1976) 4:703), β -lipotropin (Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41), magnesium pemoline (Behav Biol (1975) 15:245), -melanocyte stimulating hormone (J Pharm Pharmacol (1977) 29:110), methoximine (Pharmacol Biochem Behav (1976) 4:703), norepinephrine (Pharmacol Biochem Behav (1976) 4:703, Brain Res (1975) 84:329), orotic acid (Arch Int Pharmacodyn (1974) 211:123), papaverine (Acta Physiol Pharmacol Bulg (1976) 2:49), parachlorophenylalanine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), pargyline and pheniprazine (monoamine oxidase inhibitors, (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), pentylenetetrazol (Pharmacol Biochem Behav (1976) 4:123), physostigmine (Rosenzweig

MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), picrotoxin (Behav Biol (1977) 20:168), piperazine estrone sulfate (Curr Med Res Opin (1976) 4:303), piracetam (Psychopharmacology (1976) 49:307), progestagens (J Nerv Ment Dis (1976) 163:59), strychnine (Behav Biol (1977) 20:168, Arch Int Pharmacodyn (1974) 211:123), thyrotropin-releasing hormone (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), thyroxine (J Comp Physiol Psychol (1976) 90:1082), tranylcypromine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), uridine monophosphate (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), and vasopressin (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1).

Applicant has found that of these the literature reports that ten have been tested for treatment of Alzheimer's disease. These were ACTH 4-10 (J Clin Hosp Pharmac (1985) 10:327, Neurology (1985) 35:1348), apovincamine (J Clin Hosp Pharmac (1985) 10:327), magnesium pemoline (Lipton MA, DiMascio A, Killam KF, eds., Psychopharmacology: A Generation of Progress, Raven Press, New York, 1978, p. 1525), methylphenidate (amphetamine modified to reduce peripheral side effects (Psychopharmacology (1977) 52:251, J Am Geriatr Soc 1977 25:1), monoamine oxidase inhibitors (J Am Geriatr Soc 1977 25:1), papaverine (J Clin Hosp Pharmac (1985) 10:327), pentylenetetrazol (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177.), piracetam (J Clin Hosp Pharmac (1985) 10:327, Am J

Psychiat 1981 138:593), tyrosine (increases norepinephrine, J Am Geriat Soc (1977) 25:289), vasopressin (J Clin Hosp Pharmac (1985) 10:327, J Am Geriat Soc (1977) 25:289, Neurobiology of Aging (1985) 6:95) and physostigmine as discussed above.

With the exception of physostigmine, none of these was reported to be effective in treating Alzheimer's disease.

As shown from the literature references submitted with the response, the effective treatment of Alzheimer's disease has proved to be very difficult. Many approaches have been tried. None has been successful. Galanthamine and its properties have been known for many years. No one has previously suggested that it should be used to treat Alzheimer's disease. Many drugs having similar properties to galanthamine have been tried unsuccessfully. Under these circumstances, it is quite clear that it could not possibly be obvious to one skilled in the art to use galanthamine to treat Alzheimer's disease.

In view of the foregoing, reconsideration of the 35 USC 103 rejection is respectfully requested.

Respectfully submitted,

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